Reviewer Report

Title: Compartment and Hub Definitions Tune Metabolic Networks for Metabolomic Interpretations

Version: Revision 1   **Date:** 9/27/2019

Reviewer name: Shen Tong

Reviewer Comments to Author:

The authors managed to answer the reviewer's concerns and reflect in the context. As excluding compartment and hub information obviously simplify the global complexity of metabolic networks, thus able to provide a different perspective to network representation. Always good to see multiple complementary and robust (must be) ways to stratify large omics data. Therefore, I am FOR the option to at least provide users with include/exclude option, to suit more diversified research needs, possibly essential for those studies on intermediate metabolites, compartment-specific, or transporters.
Initial compilation had a good various coverage on databases beyond only KEGG and HMDB reactions. Good to see that the authors discusses the enrichment analysis that is prone to over-fitting versus reaction-based modeling approach in this study.
The authors also put efforts to discuss the performance between MetaboNet and other existing similar approaches, as well as to enhance the reproducibility of outcomes especially by different users in their GitHub repository. Yet the latter might be worth mentioning in the discussion section as a robustness argument.
The context is explained with much better logic and conciseness.

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